REMARKS

Claims 1-11 are pending in this application. Applicants respectfully submit that the current claims are patentable without amendment and respectfully request reconsideration and allowance of all pending claims.

RCE

Applicants note with appreciation the indication that the RCE has been accepted and that the finality of the previous Office Action has been withdrawn.

The Action does not reiterate the prior obviousness rejection based on the NORDETTE monograph (Physicians' Desk Reference, 50th Edition, 1996, pages 2755-2758), the ALESSE monograph (electronic Physicians' Desk Reference, April, 1997) in view of Katzung (Basic & Clinical Pharmacology, 6th edition, 1995, page 620) and Endikrat et al. (Contraception, 1997; 55(3):131-137). It is Applicants' understanding that these rejections have been withdrawn in favor of a new rejection.

Rejection Under 35 U.S.C. § 103

The Action again relies on Endikrat et al. in combination, this time, with Hodgen, U.S. Patent No. 5,552,394, and Katzung to allege an obviousness rejection under 35 U.S.C. § 103. Applicants reiterate their previously presented comments with respect to Endikrat et al. and respectfully request reconsideration in light of the further comments herein.

Applicants respectfully assert that the Action's continued reliance on Endikrat et al. is misplaced. The intent of Endikrat et al., as clearly stated throughout the reference--most prominently in the title, is to evaluate the efficacy, cycle control, and tolerance of 20 μg EE

treatments compared to 30 μg EE treatments over a twelve cycle treatment period. In both treatment regimes, the level of spotting and breakthrough bleeding was significantly higher in the initial cycle than in subsequent cycles. However, reduced spotting and breakthrough with steroid doses of 30 μg EE is shown when compared to 20 μg EE doses. Nevertheless, Endikrat et al. concludes that the 20 μg treatment regime "neither compromises contraceptive reliability nor leads to clinically unacceptable cycle control" (p. 136, col. 2, last paragraph). Tolerance was similar in both treatment regimes. Endikrat et al. continues, stating the

> potential advantage of the low hormone content might outweigh in part the less favorable bleeding pattern. Following the trend to further reduce the hormone dose, the 20 μg EE2 oral contraceptives could be administered in the first line. For women having a history of cycle control problems or for women having experienced such problems under a 20 μg EE2 preparation, preference should be given to the 30 μg EE2 drug.

As noted, Endikrat et al. sets forth and follows the conventional wisdom to administer as low a dose as possible, and therefore suggests beginning treatment with a low dose and increasing it only when necessary--that is if control or bleeding problems persist beyond the initial cycle(s) where it is expected. This conventional wisdom is the ***exact opposite*** of the treatment regime facilitated by Applicants' claimed contraceptive kit. Applicants' claimed kit provides higher doses of steroid in the initial cycle(s), where increased incidence of spotting and bleed through is expected. This is followed by reduced steroid levels in subsequent cycles, where lower incidence of spotting and breakthrough is expected. Endikrat et al. teaches away from treatment regimes and kits that facilitate administration of relatively high doses of steroid in initial cycles followed in subsequent cycles by relatively low dose administration. Teaching away is strong evidence of non-obviousness. For this reason alone, the rejection should be withdrawn.

Only Applicants appear to be unwilling to accept increased levels of spotting and breakthrough bleeding during the initial cycle(s) and address the issue. Absent Applicants' teaching, the Action cannot, and does not, point to any teaching, suggestion, or motivation to administer relatively high dose (e.g. 30 μg EE) compositions during the initial cycles followed by relatively low dose (e.g. 20 μg EE) compositions in subsequent cycles or to package the oral contraceptives in cycle kits to facilitate such administration. Endikrat et al., as discussed in Applicants' previous responses, simply does not teach or suggest such a treatment regime. Accordingly, the obviousness rejection should be withdrawn.

The newly cited Hodgen reference similarly does not contain any such teaching that would lead one skilled in the art to change the steroid dosage, especially from high to low, from one cycle to the next during the course of treatment. The disclosure of Hodgen compares the administration of ***consistent*** low doses of oral contraceptives over three consecutive 28 day cycles, where one test group is administered the oral contraceptive for 21 days of each 28 day cycle and a second test group is administered the oral contraceptive for 24 days of each 28 day cycle; on the remaining days a placebo was given. As with Endikrat et al., the initial cycle revealed greater incidence of spotting and breakthrough bleeding. In subsequent cycles, where the oral contraceptive dose was consistent with the initial cycle, lower levels of breakthrough and spotting were seen in both groups compared to the initial cycle. Lower levels were seen in subsequent cycles of the 24 day treatment cycle when compared to the 21 day treatment cycle. Hodgen teaches that the longer 24 day treatment regime results in lower breakthrough and spotting levels, after the initial cycle. At no time were any test subjects from either group switched from a relatively high dose to a relatively low dose, the dose was constant from cycle to

cycle. Hodgen, like Endikrat et al., notes the desire to reduce the overall hormonal intake indicating that even with the longer 24 day treatment cycle, the lower dose still provides a significant reduction in hormone intake over an annual treatment period. There is nothing in Hodgen that would teach or suggest that the dose should be altered, in any way, let alone from high to low, from one cycle to the next.

Hodgen and Endikrat et al. have several things in common. Most importantly is that in each case, in each study, each patient was administered an oral contraceptive from one cycle to the next having an identical content as the oral contraceptive administered in the first month and every month thereafter during the treatment. Both recognize that with low dose treatment, the initial treatment cycles, and particularly the first cycle, suffer from relatively high incidence of spotting and breakthrough bleeding. Both also appear to recognize that despite this problem, the benefits of the low dose treatment outweigh the problem, in light of the overall acceptable levels of spotting and breakthrough bleeding, cycle control, and contraceptive efficacy. Thus, neither suggests altering treatment of the initial cycle(s) to overcome the expected higher incidence of spotting and breakthrough bleeding.

Accordingly, neither reference alone or in combination teaches or suggests that the dose should be altered from cycle to cycle, except where the dose is increased to overcome cycle control problems as taught by Endikrat et al. There simply is nothing in the art of record teaching or suggesting anything other than giving a patient in later cycles the same or greater dosage as in the initial cycle(s).

Further, none of the references teach or suggest multi-cycle oral contraceptive kits, regardless of dosage. Even if the contraceptives employed by either reference were packaged in

a multi-cycle kit, according to their teachings, the dose would be identical from one cycle to the next, unlike Applicants' claimed kit where "the effective dosage of steroid in the penultimate cycle pack [is] greater than the effective dosage of steroid in the last cycle pack" as presently claimed in independent claim 1. Only through ***impermissible*** hindsight using Applicants' specification as a blueprint can one skilled in the art pick and choose such a treatment regime from the teachings of Endikrat et al. and Hodgen.

Applicants respectfully submit that in light the above discussion, the Action does not set forth a prima facie case of obviousness, since there is no showing of any motivation in any of the references, that would lead one skilled in the art to modify the teachings of the references to result in a treatment regime and/or kit for facilitating the treatment regime, where the dose in the initial cycle(s) is relatively high followed by relatively low doses in later cycles, as taught by Applicants.

This reply is fully responsive to the outstanding Office Action. Applicants respectfully assert no fee is due. Nonetheless, the Commissioner is hereby authorized to debit Deposit Account No. 50-1275 for any fee due or to credit said account for any overpayment.

Applicants respectfully request withdrawal of the rejection. Early reconsideration and allowance of all pending claims is respectfully requested. The examiner is requested to contact the undersigned attorney if an interview, telephonic or personal, would facilitate allowance of the claims.

Respectfully submitted,

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